
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Adolescent Health 69 (2021) 878–880

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Commentary

# How Can We Best Use COVID-19 Vaccines in Adolescents? An International Perspective

Youjia Zhong, M.Med. (Paed) [a], Le Ye Lee, M.Med. (Paed) [a,b,*], Paul Ananth Tambyah, M.D. [c], Woei Kang Liew, M.Med. (Paed) [d], and Bee Wah Lee, M.D. [a]

[a] *Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*
[b] *Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore*
[c] *Infectious Diseases Translational Research Programme, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*
[d] *Paediatric Allergy Immunology Rheumatology Centre, Mount Elizabeth Novena Hospital, Singapore*

Mass vaccination of the world population is our ticket out of the coronavirus disease 2019 (COVID-19) pandemic. We are fortunate that many efficacious vaccines against COVID-19 have been produced in less than 1 year since the first case was reported in China, and countries have launched successful population vaccination campaigns resulting in >50% vaccination rates in Israel, the United States (US), the United Kingdom (UK), Germany, Italy, Singapore, and so on by the time of writing this article in July 2021. Since the publication of the phase III trial for BNT162b2 mRNA vaccine (produced by Pfizer-BioNTech) in 12- to 15-year-olds demonstrating 100% efficacy at preventing symptomatic COVID-19 infection [1], this vaccine has also been rolled out among adolescents in Israel, US, Italy, Singapore, and so on. Countries such as UK and Germany, however, have opted to limit vaccination in adolescents to those at high risk of severe COVID-19. Here, we discuss the risk-benefit ratio of vaccinating healthy adolescents against COVID-19 at the present time and some of the ethical considerations surrounding this practice.

## Risk-Benefit Ratio

Among the high Human Development Index (HDI) countries, the risk of severe COVID-19 in children and adolescents is low, with a mortality of 1–2 per million population [2]; this is similar to seasonal influenza, for which mortality in persons younger than 21 years is 2 per million. The incidence rate of symptomatic COVID-19 in adolescents was 23,000 per million in the US at the peak of the pandemic between 1 January 2021 and 31 March 2021 [3]; of these, 64 required treatment in the intensive care unit [4] (Table 1) [1–8]. Risk of severe disease depends on individual risk factors. Within the pediatric age group, apart from infants, the greatest risk factor for severe COVID-19 or mortality is underlying medical conditions including chronic lung disease, obesity, neurologic diseases, and cardiovascular diseases. In addition, psychiatric disorders have also been associated with COVID-19-related morbidity and mortality [9]. Specifically, among adolescents hospitalised for COVID-19 in the US, 70.6% had at least one underlying medical condition [4]. Another major concern for COVID-19-associated morbidity in children and adolescents is the Multisystem Inflammatory Syndrome in Children (MISC); the incidence of which among 12- to 15-year-olds is 15–22 per million persons [8] (Table 1). Furthermore, there are indirect health effects of the pandemic on youth and adolescents, such as interrupted education and, concerningly, mental health issues associated with social isolation [10,11].

Of concern are the emerging safety signals from the BNT162b2 vaccine in adolescents, which were not detected in the trial because of the relatively small sample size of 1131 vaccinees as it was initially designed as an immuno-bridging trial. The US Vaccine Adverse Event Reporting System has detected a perimyocarditis rate of 8–10 per million second doses in girls and 56-69 per million second doses in boys [5] (Table 1). The incidence of perimyocarditis during the postvaccination period was elevated compared to that in the previous years in Israel [7]. Detailed reports of 14 cases show that perimyocarditis developed among previously well adolescent males within 4 days of receiving the vaccine, usually after the second dose [6,7]. Nine of the 14 patients (64%) required admission to the intensive care unit. Fortunately, all in these 2 case series recovered from the acute episode; however, whether long-term sequelae are possible is unknown [6,7].

Thus, on an individual patient basis, the risk-benefit ratio for vaccinating healthy adolescents for the prevention of severe COVID-19 is currently equivocal (Table 1). This is influenced by

**Conflicts of interest:** All authors declare that they have no competing interest to declare.
**Data sharing:** The data were taken from the published literature. The details of all such literature used are included in the article.
**Ethical approval and patient consent:** Not applicable.

* Address correspondence to: Le Ye Lee, M.Med. (Paed), Department of Neonatology, National University Healthcare System (NUHS), 1E Kent Ridge Road, Singapore 119258.
*E-mail address:* paelly@nus.edu.sg (L.Y. Lee).


https://doi.org/10.1016/j.jadohealth.2021.08.014

**Table 1**
Incidence rates of symptomatic and severe COVID-19 in 12- to 15-year-olds in the US, between 1 January 2021 and 31 March 2021 as reported by the Centers for Disease Control and Prevention [3,4], with mortality rate taken from longitudinal data as there were no deaths in this particular period [2,3], vaccine efficacy for various clinical endpoints [1], and the risk of myocarditis associated with mRNA COVID vaccination for 12- to 15-year-olds as reported in the US Vaccine Adverse Event Reporting System (VAERS) up to 23 June 2021 [5], with accompanying risk for severe disease [6,7]

| Clinical outcome | Incidence rate of COVID-19 in 12- to 15-year-olds in the US, per million | Vaccine efficacy in 12- to 15-year-olds | Risk associated with mRNA COVID vaccination in 12- to 15-year-olds, per million second doses |
|---|---|---|---|
| Symptomatic disease | 23,000[a] [3] | 95% [1] | Perimyocarditis [5]:<br>In girls: 8-10<br>In boys: 56-69 |
| Severe disease requiring intensive care unit admission | 64[a] [4] | 100% [1] | Perimyocarditis[c] [6,7]:<br>In girls: 6<br>In boys: 43 |
| Mortality | 1-2[b] [2] | 100% [1] | Unknown |
| Multisystem Inflammatory syndrome in Children (MISC) | 15-22 [8] | Unknown | Unknown |

[a] These numbers were taken from the peak of the pandemic 1 January 2021 to 31 March 2021.
[b] There were no deaths in 12- to 15-year-olds reported during the peak of the pandemic 1 January 2021 and 31 March 2021, so an average mortality rate over a longer period of time was used.
[c] The percentage of perimyocarditis cases requiring intensive care unit (ICU) admission was taken from 2 case series, wherein a total of nine of the 14 patients (64%) required ICU care.

the presence of comorbidities and gender [3–5]. How vaccination might influence the occurrence of severity of MISC is unknown [12]. In fact, Multisystem Inflammatory Syndrome in Adults (MISA) has been reported to occur after mRNA COVID-19 vaccination, followed by exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [13], so MISC/A remains a possibility with or without vaccination, so long as the virus is still circulating. Frenck et al. argued for the universal vaccination of adolescents because “their vaccination may prevent disease and contribute to herd immunity” [1]; this has been echoed by policy-makers. However, this may not be correct; first, as risk of transmissibility of COVID-19 increases with age [14], the population benefit of vaccinating healthy children and adolescents may be low, especially when persons in the community at high risk of severe disease have been vaccinated.

Above and beyond the medical considerations, we must keep in mind that nonmaleficence is the first medical ethics principle; as such, the practice of vaccinating healthy adolescents mainly for the benefit of others should only be considered when the vaccine has been proven to have an impeccable level of safety. This is not the current case.

## Proposed Interventional Trials

To address these data gaps, we propose the following targeted interventional trials in the pediatric to adolescent age groups:

1. The immunogenicity of the BNT162b2 was 1.76 times higher in adolescents than that among young adults [1]; as perimyocarditis is an inflammatory condition occurring after vaccination, could dose reduction in adolescents increase safety? After all, phase I trials showed that 10 mcg elicits good antigen-binding IgG and virus-neutralizing responses in young adults aged 18–55 years, comparable to the responses 30 mcg elicits in older adults aged 65–85 years. Children are not small adults but immunologically distinct; we propose studying the effects of dose reduction of mRNA vaccines in adolescents even if body weight does not differ from adults.
2. All three patients with MISA after COVID-19 vaccination were Asian or Hispanic [13]. As perimyocarditis has been suggested to be related to MISA/C in its pathophysiology, could it be more prevalent in non-white populations? The risk-benefit ratio for each ethnic group is different, as risk of severe COVID-19 has been shown to differ greatly by ethnicity. Frenck et al. recruited 85% white vaccinees in their trial [1]; we propose studying a more ethnically diverse population to look for differences in both immunogenicity and reactogenicity.
3. As the risk of perimyocarditis exists mainly after dose 2, could we avoid dose two of the vaccine for children and adolescent who are convalescent from COVID-19, as is suggested for convalescent adults? Children and adolescents are more likely to be asymptomatic from COVID-19 infection than adults, so history alone may not approximate the serological status. In locations where there have been large waves of COVID-19 and, thus, many children who seroconverted without clinical symptoms, we propose trials to investigate the strategy of point-of-care verification of seroconversion, followed by withholding the second dose for seropositive children.

These measures of dose reduction and rationalization for convalescent adolescents would also simultaneously increase availability of vaccines for the low-to-middle HDI countries, where many populations who are at risk of severe COVID-19 currently have no access to effective vaccines at all. Allocating vaccines to all healthy children and adolescents in high to very high HDI countries further worsens the inequality in vaccine distribution around the world.

## Proposed Clinical Approach

As for clinical practice, countries must weigh the risk-benefit ratio of vaccinating adolescents and children in their populations carefully and keep in mind that vaccinating the pediatric population mainly to achieve herd immunity requires a high bar of safety for the vaccines to remain ethical. Currently, both the World Health Organisation and UK’s Royal College of Paediatrics and Child Health have recommended that vaccination only be

undertaken for adolescents who are at high risk of severe disease, for example, those with obesity, chronic cardiopulmonary or neurologic disease, and severe mental illness [9]; this is a prudent stance in the light of current available evidence. A nuanced approach, taking into consideration individual risk factors such as gender, past medical history, and ethnicity, may also be wise to ensure that the risk-benefit ratio for every adolescent is accurately determined. For countries who choose to vaccinate adolescents at the same schedule and dose as adults, we propose tight monitoring of serious adverse events, with a view to re-evaluate the policy as data emerge.

## Acknowledgments

The authors wish to thank Dr. Dimple Rajgor for helping with reviewing, formatting, and submission of the manuscript for publication.

Authors' contributions: Y.Z., W.K.L., and B.W.L. contributed to designing the study. Y.Z. and L.Y.L. contributed to acquisition and analysis of data. All authors contributed to interpretation of data. Y.Z. drafted the work. L.Y.L. and P.A.T. contributed to conception of the work. L.Y.L., P.A.T., W.K.L., and B.W.L. substantively revised the work. All authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study) and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

## Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

[1] Frenck RW, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med 2021;385:239–50.
[2] Bhopal SS, Bagaria J, Olabi B, Bhopal R. Children and young people remain at low risk of COVID-19 mortality. Lancet Child Adolesc Health 2021;5:e12–3.
[3] CDC. Demographic Trends of COVID-19 cases and deaths in the US reported to CDC. Available at: https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed June 25, 2021.
[4] Havers FP, Whitaker M, Self JL, et al. Hospitalization of adolescents aged 12–17 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1, 2020–April 24, 2021. MMWR Morb Mortal Wkly Rep 2021;70:851–7.
[5] Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine Recipients: Update from the Advisory Committee on Immunization practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–82.
[6] Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics 2021;148:e2021052478.
[7] Snapiri O, Rosenberg Danziger C, Shirman N, et al. Transient cardiac Injury in adolescents receiving the BNT162b2 mRNA COVID-19 vaccine. Pediatr Infect Dis J 2021;14:e360–3.
[8] Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal distribution of US children with Multisystem inflammatory Syndrome during the COVID-19 pandemic. JAMA Pediatr 2021;175:837–45.
[9] Mazereel V, Van Assche K, Detraux J, De Hert M. COVID-19 vaccination for people with severe mental illness: Why, what, and how? Lancet Psychiatry 2021;8:444–50.
[10] Lee CM, Cadigan JM, Rhew IC. Increases in Loneliness among young adults during the COVID-19 pandemic and association with increases in mental health Problems. J Adolesc Health 2020;67:714–7.
[11] Hu Y, Qian Y. COVID-19 and adolescent mental health in the United Kingdom. J Adolesc Health 2021;69:26–32.
[12] JCVI. Joint. Committee on vaccination and Immunisation statement on COVID-19 vaccination of children and young people aged 12 to 17 years: 15 July 2021. Available at: https://www.gov.uk/government/publications/covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years-jcvi-statement/jvci-statement-on-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years-15-july-2021. Accessed July 21, 2021.
[13] Salzman M, Huang C-W, O'Brien C, et al. Multisystem inflammatory Syndrome after SARS-CoV-2 infection and COVID-19 vaccination. Emerg Infect Dis 2021;27:1944–8.
[14] Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020;26:1205–11.